REMARKS

In the Claims:

Claims 22-26 are currently pending.

Claim Rejections:

35 U.S.C. § 101

Applicants respectfully traverse the present rejections and request continued examination in light of the newly submitted evidence and arguments.

Claims 22-26 stand rejected under 35 U.S.C. § 101 for alleged lack of utility. Although the Office action acknowledges that the MLR assay is useful for screening compounds that play a role in immune response, Page 3 of the Office action mailed 9-19-07, the Office action rejects Applicants' reliance on the MLR assay in this case because allegedly "[t]he ability of the claimed protein to stimulate or inhibit lymphocyte proliferation in the MLR assay does not provide support for what specific conditions or for which specific diseases the claimed invention would predictably function for a therapeutic suppression of the immune system." Page 4 of the Office action mailed 9-1907.

Applicants respectfully disagree. It was demonstrated as early as 1995 that the MLR assay could identify molecules that could be used to suppress the graft versus host response. For example, Fung-Leung *et al. Transplantation,* 60:362-8 (1995), (previously submitted) demonstrates the ability of tepoxalin, an immunomodulatory compound, to suppress graft-versus-host reaction using the MLR assay. Fung-Leung goes on to confirm that result in *in vivo* analyses but Fung-Leung never suggests that the MLR assay *must* be confirmed by additional *in vivo* studies. Indeed, that Fung-Leung, among others, has confirmed the reliability of using the MLR assay to identify molecules that can be used as therapeutic compounds for suppressing the immune response indicates that such confirmation is not necessary for every subsequent use of MLR assay to identify immunomodulatory compounds. Indeed, US Patent No. 5,817,306 claims method of treating graft-versus-host disease using IL-1 receptor antagonists but does not disclose the results of any *in vivo* analyses. Rather, the specification explains that the

effectiveness of IL-1 receptor antagonists in graft-versus-host disease may be determined by MLR assays. In particular, US Patent No. 5,817,306 states "[t]he mixed lymphocyte response (MLR) and phytohemagglutinin A (PHA) assays are valuable for identifying immune suppressive molecules *in vitro* that are useful for treating graft versus host disease. **The results obtained from these assays are generally predictive of their *in vivo* effectiveness**." Col. 12, ll 36-41, emphasis added). Additionally, US. Patent No. 5,801,193 provides evidence that the MLR assay can be used to identify molecules useful in treating graft-versus-host disease. That patent states that "[t]he **MLR is an assay recognized by those skilled in the art as an in vitro predictor of in vivo immunosuppressant activity**." (Col. 8, ll. 8-10, emphasis added). As a final example, US Patent No 5,648,376 states that "[a] measure of immunosuppression that serves as a model for transplantation rejection is inhibition of cell proliferation in a mixed lymphocyte reaction (MLR) assay." (Col. 11, ll 24-26). Thus, the art as a whole clearly establishes that the MLR assay is a widely used *in vitro* assay for identifying immunomodulatory compounds, and that a positive result as an inhibitor of the MRL assay is accepted as valid indication of therapeutic use in the treatment of conditions such as graft-versus-host disease.

The Office action also alleges that "the results of the MLC or MLR assay in the instant specification are merely preliminary and do not support a specific and substantiality utility for the claimed invention." Page 4 of the Office action mailed Sept. 19, 2007. Applicants respectfully disagree. The specification clearly indicates that PRO361 polypeptides are useful in the treatment of undesirable immune responses such as graft-versus-host disease. The use of immunosuppressive molecules in the treatment of such disorders is well known in the art, as indicated by Fung-Leung, and US Patent Nos. 5,817,306, 5,801,193, and 5,648,376. According to Section 2164.02 of the MPEP, such evidence is sufficient to demonstrate that a positive result as an inhibitor in the MLR assay is reasonably correlated to use as a therapeutic compound for the treatment of conditions such as graft-versus-host disease.

Further, in addition to the above references and patents, Applicants previously identified two patents, US Patent Nos. 7,220,835 and 7,282,570, that are assigned to Genentech, that share specifications similar to the specification at issue and that contain claims that

rely on an assertion of utility based on results obtained in the MLR assay. The Office action rejects this evidence because "each application is examined on its own merit and support therein." However, the Court of Customs and Patent Appeals recognized that **"similar claims allowed by the Patent Office tribunals furnish evidence of what features those tribunals regard as patentable**." *In re Schecter and LaForge,* 205 F.2d 185, 98 USPQ 144, 150 (CCPA 1953). Thus, issuance of the claims in US Patent Nos. 7,220,835 and 7,282,570 based on substantially similar applications, supported by substantially identical assertions of utility that rely on results obtained from the MLR assay is persuasive evidence that should be considered in examining the presently claimed invention. In addition, the rejections of claims to PRO361 nucleic acid and polypeptide sequences in US Patent Application Serial Nos. 09/944,929 and 10/677,471 for alleged lack of utility have been withdrawn. Thus, this is additional persuasive evidence that the PTO views Applicants' asserted utility, based on the MLR assay results, as sufficient to satisfy the requirements of 35 USC § 101.

Indeed, the PTO cautions that rejections for lack of utility are rarely sustained by federal courts. MPEP § 2107.02 III B, citing *In re Gazave,* 379 F.2d 973 (CCPA 1967) (emphasis in original). The caselaw demonstrates that a utility rejection is not proper unless the PTO establishes that it has reason to doubt the objective truth of the statements contained in the written description. The PTO may establish a reason to doubt an inventor's asserted utility when:

(1) the written description suggests an inherently unbelievable undertaking; or

(2) the written description suggests a utility that involves implausible scientific principles.

In re Cortright, 165 F.3d 1353, 49 USPQ2d 1464 (Fed. Cir. 1999). The evidence discussed above clearly demonstrates that the present specification does not assert any inherently unbelievable undertaking nor does it suggest a utility that involves implausible scientific principles.

Indeed, in the present case there is no evidence that the asserted utility of PRO361, based on its activity in the MLR assay, would be considered 'false' by a person of ordinary skill in the art. Rather, as stated above, the Office has recognized that the MLR assay is art-recognized and accepted for identifying molecules that suppress an immune response. Further, in addition to explaining how to conduct the MLR assay, Example 34 of the present specification, through reference to the *Current Protocols in Immunology,* also explains how to calculate the results obtained from the MLR assay. One of ordinary skill in the art could easily carry out the MLR assay as described in the specification and *Current Protocols,* and calculate the results as taught by the specification and *Current Protocols.* Applicants have provided sufficient detail in the specification, about the MLR assay, how the assay is performed, what controls are used and how they are used, and how the data is calculated.

Moreover, at page 141 of the specification, Applicants assert that PRO361 exhibited a significant inhibitory effect in the MLR assay. That assertion is based upon the fact that PRO361 "tested positive" in the MLR assay. According to the specification the standard for identifying immunosuppressive molecules using the MLR assay is as follows: "[a]ny decreases below control is considered to be a positive result for an inhibitory compound, with decreases of less than or equal to 80% being preferred. However, any value less than control indicates an inhibitory effect for the test protein." This standard is art recognized. For example, the Declaration of Sherman Fong, Ph.D., previously submitted by Applicants with the Amendment and Response mailed September 2, 2005, provides evidence that one of at least ordinary skill in the art accepts this standard. Indeed, Dr. Fong is identified as an inventor on both U.S. Patent Nos. 7,220,835 and 7,282,570. Each of these patent documents set forth the <u>same</u> standard for assessing immunosuppressive ability of a test protein as is set forth in the present application. *See* US Patent No. 7,220,835, col. 383, ll 18-22 and US Patent No. 7,282,570, Example 9. *See also* US Patent No. 5,958,403 at col. 6, ll 16-19.

Furthermore, in light of this substantial evidence and Applicants assertion of utility in the specification based on test results of the MLR assay, no explicit data of the results of PRO361 in the MLR assay are required to demonstrate an adequate utility. In a related field, the pharmaceutical arts, practical utility may be shown by adequate evidence of

any pharmacological activity. Thus, although testing may be required to establish practical utility, that testing ***need not absolutely prove that the compound is pharmacologically active.*** Rather, all that is required is that the tests be reasonably indicative of the desired pharmacological response. In other words, there must be a sufficient correlation between the tests and an asserted pharmacological activity so as to convince those skilled in the art, to a ***reasonable*** probability, that the novel compound will exhibit the asserted pharmacological behavior. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 USPQ2d 1895 (Fed. Cir. 1996).

The present specification provides sufficient information for one of ordinary skill in the art to conclude that the MLR assay results are reasonably indicative of the asserted utility. The specification clearly states that PRO361 tested positive in the MLR assay. Significant details are provided about the MLR assay including how it was conducted, what controls were used, how those controls were used, and how the positive result was determined. The art recognizes the MLR assay as a means of identifying immunosuppressive compounds. Applicants identified patents issued by the PTO that demonstrate the PTO accepts reliance on MLR assays as sufficient evidence of utility. Applicants submitted the expert testimony of Sherman Fong, which demonstrates that one of ordinary skill accepts Applicants' assertion of utility as reasonably probable. Thus, based on this substantial evidence it is at least **reasonably** probable that PRO361 has utility as asserted by Applicants based on the immunosuppressant characteristics pr PRO361.

In view of these significant teachings and the high level of skill and understanding in the art, the lack of explicit data does not make it more likely than not that one of ordinary skill in the art would doubt Applicants' assertion of utility for the PRO361 polypeptide. This is sufficient to satisfy the utility requirement. Moreover, while Applicants have provided the Fong Declaration, which clearly states that one of at least ordinary skill in the art does not find the asserted utility to violate or contravene any established scientific principles, and have cited several patents, including US Patent Nos. 7,220,385 and 7,282,570, as evidence that Applicants' asserted utility is art-recognized and accepted, the Office has not provided any evidence showing that the asserted utility would be considered "false" by a person of skill in the art. Thus, Applicants have provided

sufficient proof of utility for claims 22-26 and respectfully request that this ground of rejection be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph:
Enablement

Claims 22-26 also stand rejected under 35 U.S.C. § 112, first paragraph because allegedly one of ordinary skill in the art would not know how to make and use the claimed invention because allegedly the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Applicants respectfully disagree. As discussed above, the claimed antibody has the specific, substantial, and credible utility of binding a polypeptide that inhibits the proliferation of stimulated T-lymphocytes as demonstrated in the MLR assay experiment discussed in Example 34 at page 141 of the application. Applicants respectfully request the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112 ¶1 for alleged inadequate disclosure on how to use the claimed invention.

CONCLUSION

Applicants believe this Request for Continued Examination fully responds to the final Office action mailed September 19, 2007. Applicants respectfully request the Examiner grant allowance of pending claims 22-26. The Examiner is invited to contact the undersigned attorney for the Applicant via telephone if such communication would expedite allowance of this application.

Respectfully submitted,

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